

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON**

**IN RE: ETHICON, INC., PELVIC
REPAIR SYSTEM PRODUCTS
LIABILITY LITIGATION**

Master File No. 2:12-MD-02327

MDL 2327

**JOSEPH R. GOODWIN
U.S. DISTRICT JUDGE**

**GENERAL PROLIFT/TVT OBTURATOR
REPORT OF ELIZABETH KAVALER, M.D.**

Prepared by

A handwritten signature in black ink, appearing to read 'Elizabeth Kavalier', with a long horizontal line extending to the right.

Elizabeth Kavalier, M.D.
New York, NY

February 27, 2016

I have prepared this Expert Report in the matter of In re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation, MDL No. 2327, currently pending in the United States District Court for the Southern District of West Virginia, before the Hon. Joseph R. Goodwin. All opinions in my report are held to a reasonable degree of medical certainty. The information contained in this report comes from my training and experience, literature reviews done on Pubmed and Ovid, journal articles, textbooks, materials provided to me by counsel for Ethicon, and the reports of Plaintiff's experts. My updated *curriculum vitae* is attached as **Exhibit A**. My CV includes a list of publications that I have authored over the past ten years. A list of materials I reviewed in forming my opinions is attached as **Exhibit B**; additional lists of materials I have reviewed are attached to my previous reports, which are attached. A list of literature I reviewed and relied upon is attached as **Exhibit C**; additional lists of literature reviewed and relied upon are attached to my previous reports, which are attached. The terms of my compensation are attached as **Exhibit D**.

I. My Background and Qualifications

After graduating from Barnard College in 1986, I worked as a public school history teacher at Christopher Columbus High School in the Bronx before entering Downstate Medical School in 1988. I completed two years of general surgery training at Mount Sinai Medical Center followed by four years of urology residency at the same institution. My training culminated in a one-year fellowship in female urology and pelvic floor reconstruction at UCLA Medical Center. Immediately upon moving back to New York, I joined New York Urological Associates, P.C., the private practice with whom I worked for 15 years, until 2015. In October of 2015, I opened my own urology practice called Total Urology Care, in New York City. I have admitting privileges to Lenox Hill and New York Hospitals, both on the upper east side of Manhattan. While at New York Urological Associates, I ran the urology residency program at

Lenox Hill Hospital for two years, from 2006-2008. For the last 10 years, I have been the Director of Urogynecology at Lenox Hill Hospital, where I am actively involved in training the gynecology residents, as well as the urology residents. At New York Hospital, I have an academic appointment and participate as the Lenox Hill Hospital site director of the fellowship program in Voiding Dysfunction, whose sites include Lenox Hill, New York Hospital – Cornell campus, and Memorial Sloan-Kettering Cancer Center.

My choice of specialty comes out of a deep commitment to women's health. In medical school, I wanted to find an area of medicine in which there was a need. I did an elective at the Mayo Clinic in Minnesota and found, to my astonishment, that female urology was the most underserved area in all of the medical fields. At the time that I passed my oral boards, there were approximately 500 board-certified women urologists in the United States out of 10,000. In New York City, there are about ten female urologists, including myself, of whom only three focus mostly on women's pelvic health. Two of us are fellowship-trained. Over 50% of the urology residencies in the U.S. do not have a fellowship-trained specialist in women's urinary health. Before the area of female urology evolved into fellowship training, interested urologists would train themselves on both the medical and surgical techniques necessary to treat women's pelvic conditions. That means that urologists need to devote significant extra time, either through self-teaching or a fellowship, to have the tools and skills to treat pelvic conditions specific to women.

Focusing mostly on women, my practice is made up of 80% female patients, ranging in age from children as young as six to elderly women in their 90s. Many of my patients feel more comfortable discussing their sexual, vaginal, and urinary problems with a female doctor. My areas of interest include urinary incontinence, pelvic floor prolapse, urinary tract infections, and pelvic pain syndromes.

I operate on about 10% of the women whom I see. The surgeries that I perform include pelvic floor repairs for prolapse, incontinence surgeries, endoscopy for stone disease and bladder tumors, and abdominal reconstructions for fistulas. Of the many prolapse and incontinence surgeries that I have performed as an attending physician, three quarters of them involve mesh. I have done more than 800 TVT-O slings and more than 500 retropubic slings. I exclusively perform midurethral sling surgeries using synthetic mesh, although I have experience with cadaveric slings, autologous slings, vaginal wall slings, and Stamey procedures, all of which I have performed in both residency and fellowship. In addition, I have performed other transobturator slings, including Monarc, Obtryx, and the Aris sling. Although I no longer use them, I have done minislings, including TVT-Secur and Miniarc.

For the anterior compartment, I have done approximately 200 native tissue repairs, 150 biological material repairs, and over 2,000 mesh repairs. For rectocele repairs, I have performed approximately 500 native tissue repairs and about 200 repairs using biologic materials. In both cases, those repairs have been done in conjunction with a mesh repair of the anterior compartment. Of the mesh repairs that I have performed, approximately 500 were performed with the Prolift kit. The native tissue repairs include Kelly plication for the anterior compartment and levator plication and perineorrhaphy for the posterior compartment. The biological materials that I have used include tissue-banked cadaveric fascia and animal products, including Repliform, Alloderm, and Pelvicol. The biologic grafts are implanted by securing the mesh to the sacrouterine or sacrospinalis ligaments. For the vault, I have performed approximately 100 McCalls culdosuspensions and 100 sacrouterine ligament fixations, using Prolene sutures and native tissue. As a surgeon involved in training residents and fellows, it is my responsibility to teach all different types of pelvic floor repairs without aligning loyalties to a

particular company or technique. I expose them to the different options so that they learn to be flexible and adaptive. Because I train residents and fellows in the operating room, I am particularly aware of the risks of surgical procedures that I teach.

II. Training for Urologists and Gynecologists

Both gynecologists and urologists perform pelvic floor surgery, which includes stress urinary incontinence and pelvic organ prolapse. Residents training in either specialty may or may not get exposure to incontinence or prolapse surgery, depending on the program in which they train. If a program has faculty members skilled in the operative techniques used to treat stress urinary incontinence or pelvic organ prolapse, then the residents in that program will learn to do the operations. If not, a resident either in urology or gynecology can spend their entire training without having seen or scrubbed into a single incontinence or pelvic organ prolapse surgery. To get experience in managing the condition, the surgeon needs to either do a post-residency fellowship, or train him or herself. Two and three year fellowships are available in both specialties, and midurethral sling surgeries are commonly taught. If a physician does not opt to spend time in a fellowship, she can learn the surgeries available to treat stress urinary incontinence and pelvic organ prolapse by enrolling in continuing medical education courses, attending cadaver labs, participating in industry-sponsored training, observing other surgeons at their facility or another facility perform the surgeries, and setting up one-on-one preceptorships. In an effort to acknowledge a certain level of proficiency in female pelvic surgery with the different methods to gaining expertise, the American Board of Obstetrics and Gynecology and the American Board of Urology started to offer a board's exam to credential practitioners in female pelvic medicine in 2013.

Regardless of whether or not a physician chooses to do a fellowship, she will need to continuously adapt her practice to the ever-advancing medical technology. Residency and

fellowship training offer the skills to operate, as well as the foundation on which to grow. It is common practice among surgeons to adapt new techniques into their treatment algorithm. Keeping up with current literature and innovations in surgery is part of our role as surgeons. Regardless of one's training and background, the only means by which new surgeries can be incorporated with confidence by a surgeon is to practice on cadavers, learn from observing experts in the operating room, and, ultimately, to operate on one's own patients. Industry-sponsored professional education such as cadaver labs with didactic sessions and hands-on labs like those offered by Ethicon offer an important method of introducing new technology. Without the ability to grow and improve on the treatments that we have learned in residency and fellowship, medicine cannot advance.

III. Pelvic Organ Prolapse

Pelvic organ prolapse is defined as the abnormal descent of the pelvic organs into the vaginal canal.¹ The vaginal canal is a potential space into which the bladder, the uterus, the small intestines, and the rectum can fall. Any single organ, or multiple organs, can prolapse. Generally, the small intestines can prolapse only if the uterus has been removed. Bladder prolapse, called a cystocele, is the most common type of pelvic organ prolapse. When the rectum prolapses, it is called a rectocele. Rectal prolapse is a different term that refers to rectal tissue pushing out through the anal canal, not the vaginal canal. When the small intestines prolapse, it is called an enterocele. Uterine prolapse has no special name.

The Women's Health Initiative has measured the incidence of prolapse in postmenopausal women. Prolapse was present in 41% of women with a uterus and 38% of women after hysterectomy. However, symptomatic prolapse occurred in only 7-23% of women.² Approximately 250,000 prolapse surgeries are performed per year. Many women with prolapse,

particularly those who suffer from milder forms of prolapse, choose not to have it surgically corrected.

A. Causes of Pelvic Organ Prolapse

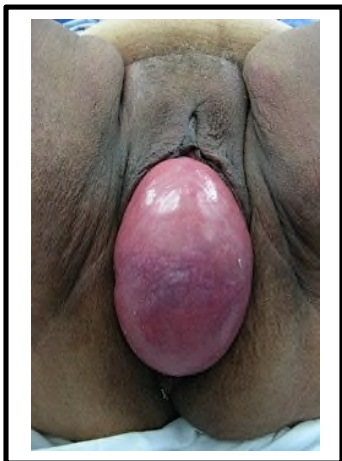
Pelvic organ prolapse can be caused by many factors. Age, hormone status, pelvic surgery, traumatic delivery, chronic constipation, obesity, smoking, and genetics all contribute to its occurrence.³ It is more common in women as they age and worsens as women age. In one scenario, after a traumatic delivery, a woman may notice that her vaginal canal is slightly more lax but the prolapse does not become obvious until she goes through menopause twenty years later. As the hormones diminish, the vaginal tissues become less elastic. In her younger years, the bladder would rest on the spongy vaginal tissues that are now less pliable. The bladder begins to sag into the vaginal canal. Pelvic organ prolapse runs in families. Many women will remember that their mother or aunt had a problem, but may not know much more than that, since these conditions are often not openly discussed. It is seen more often in different cultures and ethnic groups, such as northern European and Scandinavians, and less often in others, such as Africans and Asians. This pattern suggests that the collagen content and viscoelastic properties of the tissues differ among women of different ethnic groups. Not surprisingly, many of the surgeries that are performed have been developed in Sweden and France.

B. Grading Pelvic Organ Prolapse

When a woman presents with pelvic organ prolapse and she is examined, we grade the degree of prolapse. There are a number of different grading systems, but the two most commonly used are the POP-Q and the Baden-Walker scale. The POP-Q stands for Pelvic Organ Prolapse Quantification, and is based on measurements that are placed on a grid. The measurements include nine different values, which include three relating to the anterior vaginal wall (on top of which the bladder sits), the posterior vaginal wall (below which the rectum sits),

the apex (the top of the canal where the uterus sits, and if there is no uterus, the small intestines take over), and the distance between the vagina and rectum, called the perineum. It is frequently used in research studies. Because it is so detailed, it is now the required grading system for prolapse publications. Although the POP-Q system does not take into consideration the subjective impact of prolapse, subjective outcomes are frequently included and reported in research studies. The Baden-Walker system is based on the level to which the ball that is present in the vagina descends, irrespective of the organs involved. The Baden-Walker scale ranges from grade one (the least severe) to grade four (the most severe—where the ball is outside of the vaginal canal—see photograph below).

C. Symptoms of Pelvic Organ Prolapse



The symptoms of pelvic floor prolapse come in two forms: one is the set of symptoms related to the presence of the organ in the vaginal canal, and the second is the set of symptoms related to the malfunctioning of those organs. A woman may come in complaining that there is a ball, that looks like a baby's head, coming out her vaginal canal, especially when she bears down to defecate or when she showers. It may cause pressure, difficulty walking, bloody discharge, and vaginal irritation from the skin rubbing against itself. Sitting or lying down may relieve the pressure, but it returns with gravity. Sometimes, a woman will attempt to push it back in with her finger or even take a mirror to look at what is protruding. Dyspareunia (pain with sexual intercourse) can sometimes be attributed to the prolapse,⁴ although it is often difficult to distinguish between the physical effect of the prolapse on sexual function, the changes to the vagina as a result of aging, and the feeling of self-consciousness related to a sense of disfigurement by the prolapse. Women experiencing pelvic floor symptoms, including vaginal

prolapse and incontinence, tend to experience sexual distress more often than women without these issues.³

Symptoms related to the organ that is prolapsing include bladder issues and bowel issues. Uterine prolapse only presents with prolapse symptoms. The bladder issues that are associated with a cystocele include stress incontinence (leakage with activity, coughing, laughing and sneezing) and emptying problems. Stress incontinence and prolapse are caused by the same pathophysiology—weak pelvic floor support. Therefore, the two conditions tend to occur together. Urge incontinence, which is leakage accompanied by the urge to urinate, is the other type of urinary incontinence from which women often suffer. Urge incontinence is not generally related to prolapse.

If a woman presents with complaints of stress incontinence, and the decision is to correct the stress incontinence surgically, many pelvic surgeons will correct her prolapse as well if she has one. There are two reasons to correct a concomitant prolapse. The first is that if the urethra is supported in an effort to control her stress incontinence, but the bladder remains sagging, she will have difficulty emptying her bladder—the bladder neck will be kinked. The second reason is that the prolapse surgery is done in the same physical space. If the surgeon feels that the prolapse can be fixed safely at the same sitting, it would save the patient from a future surgery. Emptying problems related to prolapse include hesitancy, slow or intermittent flow, and incomplete emptying. If the prolapse hangs low, the bladder muscle has to work particularly hard to overcome gravity in order to empty, and obstructive symptoms may ensue. Replacing the bladder into its correct anatomic position corrects that.

Likewise, the decision to perform an anti-incontinence surgery at the time of a large prolapse repair is based on surgeon and patient preference. Women with high grade prolapse

have a high risk of developing stress urinary incontinence immediately after the prolapse repair or in the future. Immediately after the prolapse is reduced through surgery, stress incontinence can be “unmasked.” Surgeons perform urodynamic studies in an attempt to reveal occult stress incontinence, but there is no method to reduce the prolapse in a way that would parallel the surgical outcome. Many prolapse surgeons, of whom I am one, recommend performing an anti-incontinence surgery at the time of the prolapse repair, regardless of the presence of incontinence as a presenting symptom, for two reasons: 1) the risk of developing stress incontinence is high (the number cannot be quantified), and 2) the risk of the incontinence surgery is low. Any one of us who has had a patient who is *not* incontinent preoperatively and returns on a postoperative visit wet, knows how unhappy those patients are.⁵⁶

Aside from the sensation of a mass coming through the vaginal canal, symptoms of a rectocele include difficulty emptying the rectal vault. Many women with rectoceles must push their vaginal balls back into the vaginal canal in order to push their stools out. Symptomatic rectoceles are much less common than symptomatic cystoceles. It can be difficult to correlate constipation with the pelvic organ prolapse. Constipation is caused by so many different factors that isolating it to the rectocele, specifically, can be difficult.

D. Treatment of Pelvic Organ Prolapse

There are four options that a patient with pelvic organ prolapse can be offered: watchful waiting, physical therapy, a pessary, or surgery. In many cases, a woman will present to her health care provider having found the prolapse herself only wanting to know what it is and if it is harmful. Once she is educated regarding its presence, which organs are involved, how dramatic the descent is, and what her prognosis is, she may be fine living with it. The initial shock of discovering it may subside and her actual bother from it may be tolerable. The degree of

prolapse may not always correlate with the amount of bother. A woman with a grade three cystocele may be minimally bothered while a woman with a grade two is greatly bothered.⁷

This chart summarizes the reasons to correct pelvic organ prolapse:

Prolapse symptoms are bothersome	Bladder symptoms are bothersome	Rectal symptoms are bothersome
Pressure Irritation Presence of a ball in the vagina Dyspareunia	Stress Incontinence <ul style="list-style-type: none"> • Leakage with activity 	Constipation <ul style="list-style-type: none"> • Pushes to empty • Puts finger in the vagina to empty bowels
	Emptying Problems <ul style="list-style-type: none"> • Hesitancy • Intermittent flow 	

1. Non-Surgical Treatment of Pelvic Organ Prolapse

Physical therapy, also called pelvic floor therapy, has been reported to improve prolapse symptoms in some women.⁸ Techniques that are employed include biofeedback, electrical stimulation, and vaginal weights. Focused and directed therapy combined with a diligent patient may result in symptom reduction that will avoid need to use a pessary or surgery. In many cases, if stress incontinence is present, that may improve as well.

If the prolapse is bothersome, a pessary is the next option to consider. A pessary is a rubber device that is inserted into the vagina to support the prolapse. Available in a variety of shapes and sizes, the pessary needs to be removed, cleaned, and reinserted regularly. Some women are able to manage the pessary on their own, while others need to see the gynecologist every two to three months for a cleaning. Pessaries have the advantages of being minimally invasive—no surgery needed—and effective in reducing the bulge. The disadvantages are that it

needs to be removed and cleaned regularly; it creates discharge, which can be unpleasant; it needs to be removed for sexual activity; and it can unmask stress incontinence. With repositioning of the bladder, the suboptimal suburethral support is unmasked, and leakage will result. There is no option to address the stress incontinence except for wearing a pad. A woman who is not in a position for surgery personally, psychologically, or physically, can opt for a pessary. In many cases, a woman can learn to manage the pessary on her own.

Pessaries work best in women with cystoceles, or anterior wall prolapse. The pessary sits behind the pubic bone and tucks under the prolapse, reaching all the way up to the top of the vagina, called the apex. If the apex is descended, the pessary cannot sit high enough to remain in place and is easily pushed out during a bowel movement or heavy activity. Posterior wall prolapses are not well supported by a pessary because the pessary fits under the anterior wall, not the posterior vaginal wall. The best that the pessary can do for women with an apical or posterior defect is to support the anterior wall and passively support the other walls. High-grade prolapses that involve anterior wall, posterior wall, and apical descent generally do not respond well to a pessary. In these cases, if a woman is bothered and wants intervention, surgery is her only option.

2. Surgical Treatment of Pelvic Organ Prolapse

Patients often choose surgical intervention for pelvic floor prolapse primarily for the following reasons:

- The patient is bothered enough by the symptoms that she wants something done;
- Stress incontinence surgery is being done and the prolapse is corrected at the same time;
- The degree of prolapse is so high that the ureters and kidneys are obstructed;

- The vaginal mucosa overlying the prolapse is getting ulcerated from rubbing;
- For anterior wall prolapse, the bladder is not emptying completely, leading to urinary retention and urinary tract infections;
- In isolated posterior wall defects, the bulge is symptomatic or defecatory issues are directly related to the prolapse; and
- To address a recurrence of prolapse following a prior failed surgical repair.

In all of these situations, a pessary will not work and surgery has to be considered.

In considering which surgical approach to use, three decisions need to be made, depending on the patient's comorbidities, the surgeon's experience, and the physical presentation of the prolapse: (1) the abdominal versus the vaginal approach; (2) if the vaginal approach is elected, whether or not mesh should be used (in the abdominal approach, mesh is nearly always used); and (3) whether the patient should have a hysterectomy.

a. Surgical Treatment: Abdominal v. Vaginal Approach

1) The Abdominal Approach

The abdominal versus the vaginal approach refers to the cavity through which the surgeon will access the prolapse. In the abdominal approach, the surgeon will get to the pelvic floor prolapse from above and work his/her way down into the pelvic cavity and vagina, through a procedure called an abdominal sacrocolpopexy. There are three methods of accessing the abdominal cavity: **open** (by making an incision, usually at the bikini line); through a **laparoscope** (which involves creating three 1½ inch holes in the skin and muscles of the abdomen through which long instruments can be placed in order to perform the surgery); or with a **robot** (in which five 1½ inch incisions are made through the abdominal wall skin and muscles

through which long instruments can be placed to perform the surgery). Robotic sacrocolpopexy is a relatively new procedure that has only come into the mainstream in the last several years.

In all of the abdominal approaches, the same techniques are applied. The small intestine and large intestine are in the field and need to be packed out of the way in order to avoid injury. The posterior peritoneum (the back wall of the bag that holds the intestines) is identified and opened in order to reach the uterus and bladder. A hysterectomy is usually performed if the patient still has her uterus, but not always. Either the vaginal cuff (if a hysterectomy is performed or has been in the past) or the body of the uterus or cervix (if a supracervical hysterectomy is performed) is attached to the sacral promontory. A large plexus of nerves and blood vessels sits at that site. Care must be taken to avoid these structures or bleeding and nerve damage can ensue.

Polypropylene mesh is used to secure the vaginal cuff, the cervix, or body of the uterus to the sacral promontory. In some techniques, the dissection can extend into the anterior or posterior vaginal wall, which is lifted off the bladder or rectum. The mesh is laid into the space that is created in order to provide direct support under the prolapse. By attaching the mesh to the cuff and the sacral promontory only, the anterior or posterior prolapse may be corrected secondarily, without the extension of mesh under the vaginal mucosa. The apex will be well supported, which may passively pull the anterior and posterior walls into their proper anatomic position, but sacrocolpopexy does not provide primary support to the anterior or posterior vaginal wall.

Tacking the apex of the vagina to the sacrum will support the top of the vagina, but in high-grade prolapses, the anterior wall may still not be well enough supported to eliminate a symptomatic bulge. In order to repair a cystocele from the abdominal approach, surgeons have

two options. They can either do a paravaginal repair, which does not involve mesh, or they can make a tunnel between the vaginal canal and the bladder and lay mesh in that space. Surgeons who do not like to use mesh in the vagina may opt to do a paravaginal repair, which involves imbricating, or over-sewing, the tissue next to the anterior prolapse in order to tighten the lateral aspect of the vaginal wall. By pulling up the lateral support, the vaginal mucosa will tighten and the prolapse will lift up. Again, this is a passive correction, not a direct repair of the defect that sits under the bladder. A rectocele cannot be corrected from the abdominal approach.

Open sacrocolpopexy, which is the name used to describe the procedure in which an incision is made in the abdomen and mesh is attached to the body of the uterus, the cervix, or the vaginal cuff to the sacral promontory, is called the gold standard for apical prolapse repair. It is the form of surgical repair that has been used the most and we have the most data regarding its success and complications. Although it is a successful operation for apical prolapse, open sacrocolpopexy is invasive and exposes patients to all of the potential complications of abdominal surgery. A meta-analysis looking at studies published from 1966 to 2004, in which the data was followed for, at least, six months, and at most, three years, found that apical support was maintained in 78-100% of patients, and prolapse was repaired in 58-100% of patients. Mesh erosion at the cuff occurred in 3.4% of the cases and small bowel obstruction requiring surgery occurred in 1.1%.⁹ In another study, gastrointestinal complications following abdominal sacrocolpopexy were reported in 20/322 patients. Eighteen percent reported nausea, vomiting, bloating, and ileus during the initial hospitalization, and 9.8% had persistent symptoms at six weeks. Over 5% needed to be readmitted for ileus or small bowel obstruction, in whom 1.2% required surgical intervention. Three percent were managed medically.¹⁰

In order to utilize the latest technology, laparoscopic and now robotic sacrocolpopexy has become more available and popular. These surgeries use the principles of open sacrocolpopexy with an effort to reduce the morbidity associated with an incision. Internally, the surgery is the same—the abdominal cavity is accessed, the bowel is reflected out of the field, and the uterus, cervix, or vaginal cuff is pulled up to the sacrum and fixed with mesh. The robotic approach has been written about extensively, with the authors self-reporting their techniques and outcomes. Surgical times are longer for robotic surgery, ranging from 1½ hours to over four hours, not including the sling, if that is planned. However, blood loss and hospital stay are shorter for robotic surgery.¹¹ Complications of robotic surgery include bleeding, injury to abdominal organs, mesh erosion, and complications related to the hysterectomy. Most robotic surgeons perform supracervical hysterectomies in conjunction with the prolapse repair in order to reduce the risk of re-prolapse (if the uterus is left in place) and mesh erosion (if the cervix is removed). In one study, mesh erosion rates in robotic-assisted sacrocolpopexy were reported at 0% in women who had a supracervical hysterectomy and 3-37% in women who had a total hysterectomy. This broad range of erosion rate is related to the type of synthetic mesh that was used. In the group who had a supracervical hysterectomy, three had abnormal pathology in the body of the uterus, including endometrial adenocarcinoma and focal hyperplasia with atypia.¹² Management of these findings was not reported.

2) The Vaginal Approach

The vaginal approach to prolapse repair has been explored in order to eliminate the potentially life-threatening complications that abdominal surgery entails, including bowel injury and vascular injury. Not only are the abdominal organs avoided, but also the prolapse can be accessed directly through this natural orifice. Through the vaginal canal, retractors are placed to expose the field and a full-thickness incision is made in the vaginal mucosa that overlies the

prolapse. The loose ligaments that support the pelvic organs are exposed and the prolapse can be repaired. There is scientific debate as to the best method in which to repair the prolapse if the vaginal approach is used. The three options for reducing the prolapse include the imbrication of the native tissues (the traditional repair), the insertion of biocompatible materials (xenograph repair), or the attachment of synthetic mesh (mesh repair).

Imbrication (also commonly referred to as colporrhaphy), which is the traditional method of repairing pelvic floor prolapse, involves grasping tissue on the side of the defect and pulling it into the center, securing it with sutures, and tapering the vaginal mucosa in the closure. Failure of this technique approaches 50% at one year in patients with grade two or higher prolapse repairs, which is why alternative procedures have been developed.¹³¹⁴

Xenografts are biocompatible materials from animal tissue, often from pigs (porcine) or cows (bovine). Allografts are biocompatible materials that come from donor cadavers. These materials are harvested and irradiated to eliminate any prions, or potentially infectious agents. They are processed in tissue banks without consistent quality control. Consistent tensile strength cannot be obtained with biological materials because each individual donor has tissue qualities that cannot be determined or tested. In addition, biocompatible materials can be integrated into the body and digested. In my experience of re-operating on patients who have failed xenograft repair, it is as if no surgery had been done. The native tissues are too pliable and elastic, and too easily dissected 12 months after a biological material has been implanted. Ideally, after prolapse surgery, the tissues should be fixed in their new, correct anatomic position with enough elasticity and mobility to feel natural but not enough to result in recurrence of the prolapse. Two-year outcomes were reported comparing colporrhaphy (traditional repair), porcine xenograft repair (biologic), and synthetic mesh in 99 patients. Failure of the prolapse as determined on POP-Q

exam were 58% in the traditional repair, 46% in the porcine xenograft repair, and 18% in the synthetic mesh repair. Two of the 33 patients in the xenograft repair needed a re-operation on their anterior compartment prolapse.¹⁵

Moreover, randomized controlled trials comparing native tissue surgery to Prolift mesh do not show statistically significant differences between the two repairs in terms of de novo dyspareunia, de novo pelvic pain, or sexual function. For example, in a multicenter randomized prospective controlled study of 168 patients comparing sacrospinous fixation and transvaginal mesh, patients receiving transvaginal mesh had less recurrence of prolapse (17%) compared to native tissue repair (40%). Quality-of-life scores for transvaginal mesh patients improved, as reflected by UIQ, CRAIQ, and POPIQ scores. Sacrospinous fixation had lower improvement of bowel symptoms as reflected by the CRAIQ questionnaire. This was balanced against an exposure rate of 20.8%. There was no statistically significant difference between sacrospinous ligament fixation and Prolift in dyspareunia or pelvic pain in this study.¹⁶

Another study (Svabik) reported a significantly better cure rate of prolapse using Prolift (97%) versus traditional repair (38%). Minor mesh exposure occurred at the three-month follow up in the Prolift group in three (8%) cases; two of these were resected, while the third was asymptomatic and treated conservatively. At the one-year follow-up, there was no additional case of protrusion. Five (15%) patients reported vaginal blood spotting due to granulation tissue in the SSF group, all of whom were treated on an outpatient basis. There was no statistically significant difference in dyspareunia and PISQ scores between sacrospinous ligament fixation and Prolift.¹⁷

In a retrospective trial of 524 patients from a single center with a median follow-up of three years (de Landsheere), the global reoperation rate was 11% (urinary incontinence 7%,

mesh-related complications 4%, or prolapse recurrence 3%). Surgery due to symptomatic mesh retraction was extremely rare at 0.4% (2/524), and surgery due to mesh infection was only 0.2% (1/524).¹⁸

Dietz and Maher reported the effects of pelvic organ prolapse on sexual function. With regard to the anterior compartment, the use of mesh is associated with neither a worsening in sexual function by PISQ nor an increase in de novo dyspareunia compared with traditional anterior colporrhaphy.¹⁹

Withagen examined the effects of a trocar-guided mesh compared with conventional vaginal repair in a randomized controlled trial of patients with recurrent prolapse. Anatomic failure in the treated compartment was observed in 38 of 84 patients (45.2%) in the conventional group and in eight of 83 patients (9.6%) in the mesh group ($P<.001$). Patients also reported subjective improvement. Pelvic pain and dyspareunia decreased at a similar rate at one year compared to baseline, in both groups. De novo dyspareunia was reported in 10% of the mesh group, and 8% of the Prolift group. There was a 16.9% rate of mesh exposure ($n=14$) with nine being asymptomatic. Five exposures required excision and they resolved.²⁰

Sokol reported objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse at one year. He noted that at 12 months, both groups had improvement of pelvic organ prolapse-quantification test points to similar recurrence rates. Quality-of-life scores improved and did not differ between groups: 96% mesh versus 91% no-mesh subjects reported a cure of bulge symptoms. No statistical difference existed between the no-mesh group (21%) and the Prolift group (10%) regarding new-onset dyspareunia or sexual function. There were an equal number of Prolift mesh exposures and suture erosions in the no-mesh subjects.²¹

In a randomized controlled trial comparing vaginal repair with Gynemesh PS mesh versus colporrhaphy for prolapse (Carey), the mesh group success rate at one year was 81% compared with 65% in the no mesh group. Both groups reported a high level of satisfaction with surgery and improvements in symptoms and quality-of-life. De novo dyspareunia was reported in 16% sexually active women in the mesh group versus 15% in the no mesh group. Two women in the no-mesh group required vaginoplasty for vaginal stenosis.²²

In 2011, Altman reported in the New England Journal of Medicine the results of a randomized trial of anterior colporrhaphy versus transvaginal mesh for pelvic organ prolapse. In this study of 389 evaluated at one year, the success rate was significantly higher in the women treated with transvaginal mesh repair (61%) than in those who underwent colporrhaphy (35%). The mesh-based repair also lasted longer. Surgical reintervention to correct mesh exposure during follow-up occurred in only 3% of patients in the mesh-repair group. No statistically significant difference existed in pelvic or genital pain at two months or 12 months between the colporrhaphy and mesh groups. Indeed, PISQ-12 scores improved by 2% in native tissue repairs and 2.8% in Prolift repairs. Dyspareunia was reported “usually” or “always” by 2% of the women following colporrhaphy and by 7.3% after transvaginal mesh surgery, but the rates were not statistically significantly different. Finally, patient sexual satisfaction was 48% in the Prolift group compared to only 40% in the colporrhaphy group.²³

In short, studies of Prolift involve more patients and longer follow-up than native tissue repair. The vast majority of women in these studies did not have pain after undergoing vaginal mesh surgery. Indeed, the studies show that, in some women with pre-existing dyspareunia, they experienced improved sexual function and decreased dyspareunia following a Prolift implant.

b. Surgical Treatment: Vaginal Approach, Mesh v. No Mesh

If warned, surgical complications that are correctable are generally acceptable to patients. Thirty to sixty percent failure rates for traditional repairs and 40% failure rates for xenograft materials have driven the effort to find a vaginal repair that is safe, efficacious, and durable. To this end, synthetic materials were introduced. The use of mesh to treat stress urinary incontinence (“SUI”) has been established as the gold standard. Reports from 2004 as well as longitudinal data have continued to support the use of mesh in the treatment of SUI.²⁴²⁵ Vaginal surgeons have closely observed the experience of hernia surgeons. Connective tissue laxity is implicated in inguinal hernias and hiatal hernia, as well as in pelvic organ prolapse.²⁶ Although the ideal material is still evolving, synthetic mesh is the primary method in which general surgeons repair hernias. The perfect material is still elusive in hernia surgery as well as in vaginal surgery.

The evolution of hernia surgeons’ use of synthetic mesh parallels the experience of pelvic surgeons. However, the requirements of the mesh are different for the different compartments. Pelvic repairs must have greater tensile strength in order to withstand the high intra-abdominal pressures that are generated by heavy lifting, coughing, gravity, and bowel movements. In addition, animal models have not been developed that can mimic the application of mesh in the human pelvis. Examination of the histopathology of pelvic mesh have been performed in which five different synthetic grafts were implanted into human pelvises and then explanted to study the response of the tissues.²⁷ Strength and integrity cannot be determined, but tissue integration and safety can be, which this study reflects.

The ideal graft material includes the following characteristics: non-allergenic, non-carcinogenic, easily manufactured, adaptable, inexpensive, and durable. Many different options have been proposed, but the material that encompasses the most favorable characteristics is

polypropylene, a plastic polymer than can be formed into a fabric. Its properties include elasticity without loss of integrity over time. Although similar to nylon and polyethylene, it has different qualities that, from a surgeon's perspective, make it particularly adaptable for human use. Other synthetic materials that have not been used successfully are Dacron, nylon, and polyethylene glycol.

Polypropylene is knitted into a monofilament mesh with a pore size large enough to permit macrophages, fibroblasts, and leukocytes to infiltrate, allowing for incorporation of the mesh into the native tissue, protecting from infection, and inducing neovascularization and collagen deposition. Reported in 1962, the first vaginal mesh was used by Williams and Telinde to treat stress incontinence.²⁸

The histological response to mesh is first to induce t-helper cells, which activate leukocytes to generate tumor necrosis factor- β , interferon- γ , and interleukin 12. These inflammatory cytokines activate macrophages and initiate an inflammatory process, which leads to the infiltration of capillaries and giant cells, and the creation of fibrous tissue on the external surface of the implant. Collagen replaces the fibrous tissue, incorporating the graft into the native ligaments. Different weaves of polypropylene will induce a different result. The tighter weaves and multifilament braided meshes provoke more inflammation, which can result in hardening, shrinking, and eroding of the mesh.²⁹

The four subtypes of synthetic polypropylene mesh include Type I, Type II, Type III, and Type IV. The type we use today, Type I, is a monofilament, unbraided framework with a pore size over 75 microns, which allows for infiltration of macrophages. The result is a lower rate of infection and extrusion, with a higher rate of adhesion to the neighboring tissues. Antibiotics can effectively eliminate bacteria because the medication can penetrate the pores. Type II mesh is

multi-filamentous and micro-porous with a pore size of less than 10 microns. Although adhesions are rare, infiltration of fibroblasts and neovascularity cannot occur because the pore size is too small. The infection rate is high. Encapsulation, as opposed to infiltration, occurs with Type II polypropylene mesh. Type II is a combination of small and large pore fenestrations in a multifilament weave. Examples of this type of mesh are Teflon, Dacron, and Mersilene.³⁰ Because of its microscopic pore size, Type IV polypropylene mesh forms sheets in the body and cannot be used in vaginal surgeries.

Since the first studies looking at the use of vaginal mesh were performed in 1962, many different techniques and synthetic products have been explored. Complications have included fistulas, exposures, infections, and pain. Type II and III polypropylene meshes have resulted in a much higher rate of erosion compared to Type I mesh. Efforts have been made to reduce the morbidity of mesh by introducing partially absorbable materials, which are a combination of absorbable and permanent components.

Although synthetics have been used to treat incontinence for decades, the early reports on the use of mesh for prolapse repair appears in the 1970s. Those repairs generally involve the posterior compartment and the materials include Marlex and Teflon, which are no longer used in vaginal surgery. The current wave of articles on which we have based our current materials and techniques come from studies published in the early 2000s. Most of these studies involve small numbers of patients in which the surgeon self-reports on her experience over a limited follow-up period. In 2000, a group from Great Britain reported on vault prolapse and rectocele repairs in 29 women, of whom 19 had previous repairs. At 14 months, all of the prolapses were still repaired and dyspareunia rates decreased from 38%, preoperatively, to 17%, postoperatively. One patient needed her mesh removed for infection.³¹ In 2004, 14 randomized trials were reviewed in which

comparisons were attempted to be made between open sacrocolpoxxy, traditional vaginal repair, and mesh augmented repair. While comparison of the studies presented challenges, one author concluded “the use of a polyglactin mesh overlay at the time of anterior vaginal wall repair may reduce the risk of recurrent cystocele.” Polyglactin is an absorbable mesh that is not used by most pelvic surgeons today. However, the article speaks to the need for better results using the vaginal approach, which, compared to abdominal surgery, “was quicker and cheaper to perform and women had an earlier return to activities of daily living.”³²

Eleven randomized, controlled trials and two meta-analyses comparing traditional prolapse repair with synthetic mesh repairs have been published between 2007 and 2011. Though not without their limitations, these studies help surgeons determine the methods through which they perform their surgery using the safest, most efficacious techniques. The earliest studies focused on the safety of the materials and the later studies on efficacy. Overall, most of the studies determine that mesh repairs provide better support of the prolapse by exam one year after surgery. These studies have shown success rates over a range of 93% (Hiltunen 2007) to 75% (Altman 2011) in the women who participated. There were no differences in the quality of life between the mesh groups and the traditional groups as determined by questionnaire. In other words, the mesh provided better results without compromising quality of life.³³

In 2007, Hiltunen et al. reported on their experience comparing 104 patients who underwent a traditional repair with 97 patients who underwent a mesh repair in which the surgeon self-styled sheets of polypropylene mesh. Greater than POP-Q stage II or higher prolapse reoccurred in 38% of the traditional group, and only 6.7% of the mesh group. Seventeen percent of the mesh patients had anterior vaginal wall exposures of the mesh, in which 78% underwent local excision. One patient in the traditional repair group needed to be re-operated for

recurrence.³⁴ In 2008, another study in which patients were also followed for a year reported 91% success in the mesh group and 72%, in the non-mesh group. Again, the surgeon tailored sheets of polypropylene mesh. Exposure occurred in 6.9% of the mesh group and were all treated with local excision.³⁵ Three-year data is available from a multi-centered, randomized trial involving 105 patients in whom sheets of polypropylene mesh were used versus 97 women in whom a traditional repair was performed. POP-Q stage II recurrences were seen in 13% of the mesh group and 41% of the traditional group. Eight patients in the traditional repair group required reoperation for recurrence. The authors reported a 19% exposure rate of which 70% needed the exposed mesh removed by local excision, and the remaining 30% only required topical estrogen. Both groups reported global improvement of their quality of life without differences in sexual function or pain.³⁶

The main complication of vaginal mesh in all of these studies is extrusion of the implant through the vaginal mucosa. In 2011, Maher et al., came out with two-year data from the Cochrane review of prolapse repairs performed with mesh and found that the overall erosion rate was 10%, with 6.6% requiring surgical repair.³⁷ Most of the studies published after 2007 report provide vaginal erosion rates of about 5%. These erosions all refer to exposure of the mesh in the vaginal wall. The exposure can present with vaginal discharge or discomfort with sexual activity on the part of the patient or her partner. Although unpleasant, this occurrence is minor in that it can be corrected in most cases with either vaginal creams and antibiotics, or a minor procedure in which the mesh is excised and the vaginal mucosa is left open. The excision is often performed in the office. Very few surgeons have reported the need to remove the entire mesh. Exposures can be described as a healing issue more than a problem with the mesh itself. Reoperation for

recurrence, which is seen in 30% of traditional repairs, occurs more frequently and is much more complicated to address than excising a small piece of mesh.

In my first 525 prolapse repairs using sheets of polypropylene mesh, we reported on 367 patients who were followed from six months to eight years. Surveys were sent to 568 patients of whom all 367 responded. Eleven percent of the respondents were found to have mesh exposures, all of which were corrected with excision of the mesh either in the office or the operating room. Two patients had extensive removal of the mesh due to exposure through the vaginal mucosa. Excision of the mesh did not result in re-prolapse. In all of the patients in whom I repaired the exposure, the fibroblastic response allowed for the integration of the mesh, remodeling of the underlying support of the vaginal canal, and maintenance of the repair. Now that I have employed newer techniques, I have not taken a patient back to the operating room for an extrusion in over two years.

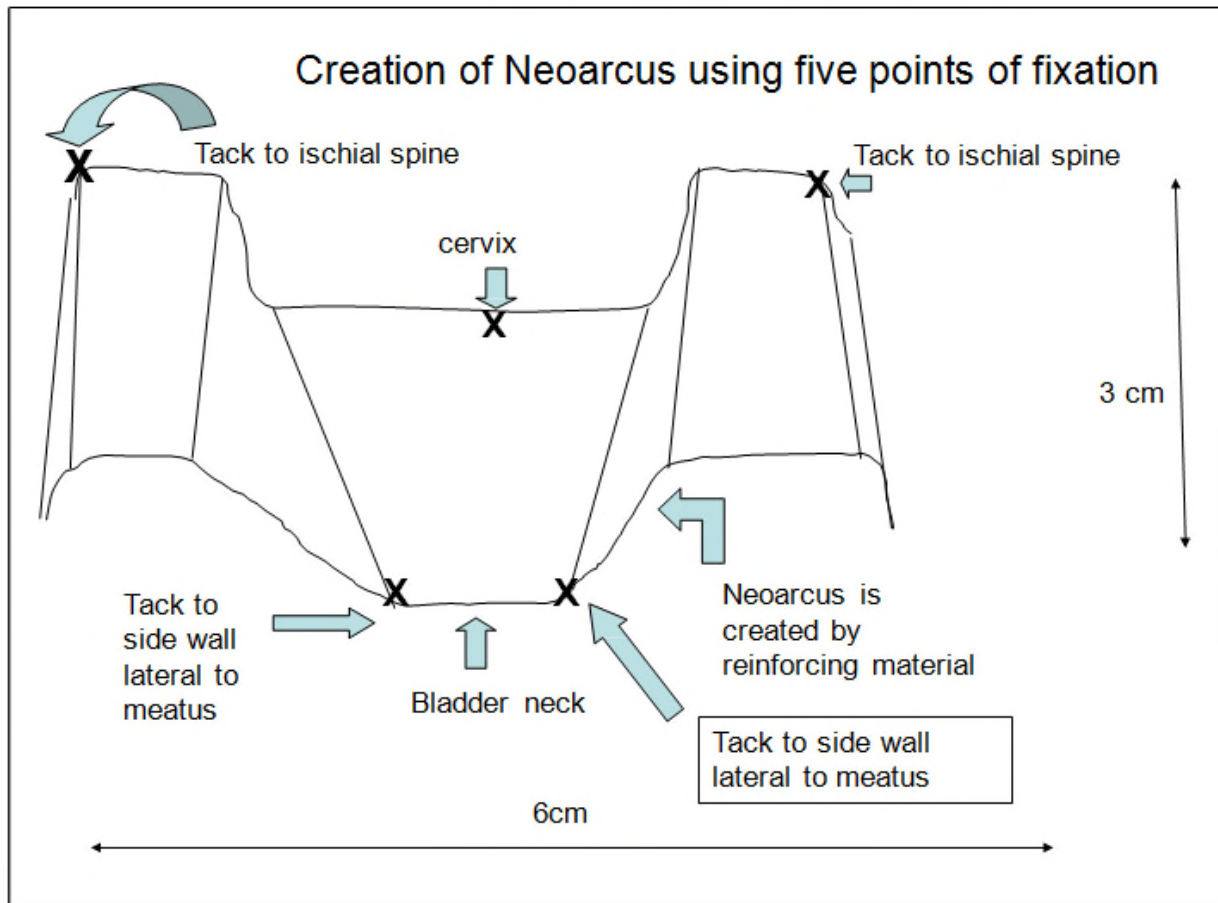
Newer techniques have helped reduce the risk of mesh exposure through the vaginal skin. Hydrodissection through the vaginal mucosa in the layer between the epidermis and the dermis creates less bleeding during the dissection. Hematoma formation behind the vaginal mucosa can force open the incision and impair healing. Full-thickness skin flaps provide a more substantial layer of tissue over the graft, which prevents button-holing of the mesh through the mucosa. Double-layer closure of the skin incision ensures against a suture rupturing and exposing the mesh, thus impairing healing.

With pelvic surgeons' growing interest in the use of vaginal mesh, mesh manufacturers began to develop kits that included delivery systems that were more favorable for implantation of polypropylene mesh. The kits provided better fixation points, tension-free repairs, and smaller incisions. The information gleaned from the use of sheets of polypropylene mesh is applied to the

mesh kits, which were viewed as the implantation of the same material with a refined delivery system. At the forefront of this burgeoning area of progress was Prolift, the product that is based on the TVM procedure that was developed and studied in Europe extensively before being introduced in the U.S.

c. The Prolift Pelvic Floor Repair System

By the time the Prolift system was introduced in the United States, I already had been using self-tailored polypropylene mesh in my prolapse surgeries for several years. In 2000, when I came out of fellowship, the only materials that were available were the mesh sheets used by the general surgeons to repair hernias. Gynemesh PS became available in 2002, so I switched to using that thinner, wider-knit option. I would fashion a 3 x 6 cm piece of mesh into a trapezoid that would sit under the bladder, lay along the side walls to create a neo-arcus tendineus, and support the apex by attaching to the sacrouterine ligaments, using vicryl sutures, large needle drivers, and big needles in order to reach the space.³⁸ To get the apex as high as possible, I would often work with palpation because I could not get retractors deep enough to visualize the sacrouterine ligaments. Risk of catching a ureter is high in this technique. Frequently, I would get stuck with a needle during the surgery. High fixation of the mesh provides better support of the apex. When the capio needle driver (Boston Scientific) became available, we were able to use that to reach beyond the sacrouterine ligament to the sacrospinalis ligament for good apical support. The risk of ureteral injury dropped but we were now managing the risk of pudendal nerve entrapment through fixation of sutures to the sacrospinalis ligament.



The limitation of this self-styled technique were threefold. First, the mesh was being tacked to the sacrospinalis ligament with only a single point of support on each side. If the sutures gave way, the repair would not hold up as high as would be desirable to prevent recurrence. The mesh itself would fix into place under the bladder and maintain central support, and the lateral fold would hold the sidewalls, but the apex would give way, resulting in uterine or apical descent. Second, the repair required a wide dissection in order to introduce the instruments. Third, because the apex was only supported with a single stitch on each side, most women with high-grade prolapses, vault prolapse/enteroceles, or uterine prolapses would not have enough support. They needed a formal vault suspension, which required either a hysterectomy or enterocele repair, with opening of the sac, reducing the contents, and repairing the defect.

Vaginal hysterectomy, which I performed myself as a urologist, and enterocele repairs, both involve opening the abdominal cavity from below. The presence of bowel in the field and the removal of a healthy but prolapsed uterus introduce morbidity that exists only because we did not have the proper materials and instruments to avoid opening the peritoneum. We needed a technique by which we could support the apex of the vagina or uterus without entering the abdomen and removing a healthy uterus, working through the natural orifice of the vagina.

Repairing high-grade prolapses with durable results has been a challenge for prolapse surgeons. Abdominal techniques had provided the best results, but the morbidity was high and nearly always involved a hysterectomy or supra-cervical hysterectomy. Robotic and laparoscopic techniques had not been widely introduced in 2005, but even now, they risk the morbidity of any surgery that violates the peritoneal cavity. Again, these require removing the uterus in total or in part. Successful vaginal reconstruction of grade four cystocele, enterocele, rectocele, and uterine descent had eluded us until Prolift was introduced.

In 2005, when the Prolift trocar kit became available, I was skeptical because I was not interested in using a kit with trays of disposable instruments that was more expensive than flat mesh. In July of 2005, I went to Allentown, Pennsylvania to learn about Prolift from Dr. Vincent Lucente. There were two or three surgeons there for a lecture, which was followed by a case in which we observed Dr. Lucente implant a Prolift mesh into a patient. Ethicon sponsored the program and Dr. Lucente lectured from the company's professional education slide deck for Prolift.

Despite my skepticism, I could not deny that the Prolift kit offered a solution to the problems that I had experienced managing high grade prolapse. After I began using the Prolift kit, I stopped routinely performing vaginal hysterectomies for grade four prolapse of any kind.

The apex is supported to the sacrospinalis ligament without fixation, so the risk of pudendal nerve entrapment is reduced. The method of drawing the straps through the superficial sacrospinalis ligament and gluteal muscles posteriorly, and the muscles of the inner thigh with the deep anterior wings, gave the apex a wide surface area of support. The kit used the same mesh that I was already using, so the mesh component was not concerning to me. Finally, at the end of the surgery, because the mesh was not fixed with sutures, it could be loosened and “sculpted” to the patient’s anatomy. Loose placement of the mesh allowed for retraction, which I was already well aware of and had been accounting for in my self-styled method. Prolift changed my surgical approach to high-grade prolapse repair. Based on my experience, Prolift also did not raise any new risks that I had not encountered with other surgeries. To the contrary, I felt that it reduced the risk of many complications. As of today, I still perform mesh repairs for both prolapse and stress incontinence.

In 2006, the one-year data regarding the results of Transvaginal mesh (TVM—the precursor name to Prolift) were reported in 175 patients at the ICS meeting.³⁹ Only three of the 83 patients with a stage three (grade three) prolapse and none of the women with stage four prolapse had recurrences. They reported a 4.8% dyspareunia rate and 7% retraction rate. Eleven of the 175 patients required mesh excision for extrusion. The techniques that were introduced through these studies included extensive hydro dissection with saline, lidocaine, or epinephrine, full-thickness skin flaps, and no tapering of the vaginal skin. These impressive results were reported in women with and without hysterectomy.

The three-year data from the prospective French TVM studies were presented at AUGS in 2008 (and were published in 2010), three years after I was already performing the procedure in women with grade three and four prolapses. In the published data, none of the patients who

initially presented with stage four and a total of four stage three patients recurred, out of a total of 72. Four of 39 sexually active women had dyspareunia and 14.4% had mesh exposure. This rate of mesh exposure was attributed to some degree to concomitant hysterectomy.⁴⁰ The five-year data from the prospective U.S. TVM studies showed a total of 20.7% recurrence with no stage three or four recurrences appearing between 3 and 5 years.⁴¹ By the time the five-year data was released in 2011, I had been doing mesh repairs for 11 years, and using Prolift for six years.

By the time that I had started using Prolift, I was familiar with mesh complications, specifically extrusion, contraction, and dyspareunia. These problems were not specific to the Prolift kit but are seen in all mesh surgeries. My reoperation for extrusion has dropped from 11% to less than 2% because I am implementing the techniques that I have learned through the Prolift experience—full thickness mucosal flaps, generous hydrodissection, and no tapering of the vaginal mucosa. Extrusions can be solved with excision of the area of mesh and allowing the vaginal mucosa to epithelialize over it. Although patients are not pleased when an extrusion is identified, it generally does not cause major upset because it is correctible. Dyspareunia can be a complicated issue. Removing the area of mesh that is tender during intercourse will usually solve the problem if it related to mesh, specifically. Other causes of dyspareunia are seen in women with high-grade prolapse, most of whom are in the menopausal age group. Multi-disciplinary intervention usually will allow them to have a functional vaginal canal after any prolapse surgery, including those performed with mesh.

Although I have instructed numerous residents and fellows at Lenox Hill and New York Hospitals on the use of Prolift, I have not served as a Prolift preceptor for Ethicon, other than serving as a proctor/preceptor to assist one physician in surgery. I have served as a preceptor on the Prosima product, which employs the same mesh as Prolift; I taught three cadaver labs over

two years, for which I was compensated. At these labs, samples of the Prolift kit were available but I did not provide instruction on the use of the product.

IV. Stress Urinary Incontinence

Urinary incontinence is defined as the involuntary loss of urine. The two main types in women include urinary urgency incontinence (UI) and stress urinary incontinence (SUI). UI occurs when the loss of urine is accompanied by the urge to urinate. The volume of leakage can range from a few drops to an entire bladder's worth of urine. SUI results when urine squirts out during an increase in intra-abdominal pressure, such as with coughing, laughing, sneezing, lifting, or bending. Approximately 65% of women with urinary leakage will have mixed incontinence, which is a combination of both stress and urgency incontinence. In a study published in the International Journal of Urogynecology in January 2014, the overall rates of urinary incontinence in women between the ages of 30 and 79 years old is 14% monthly and nearly 9% weekly.⁴² Urinary incontinence affects up to 50% of women at some point in their lives.⁴³ Of these women, 30–80% experience SUI.⁴⁴ Of the two types of urinary incontinence, urgency incontinence is the more bothersome condition, according to a study published in European Urology in 2014 looking at lower urinary tract symptoms in 3,727 men and women aged 16-79.⁴⁵ However, the bother to a particular woman is specific and needs to be considered.

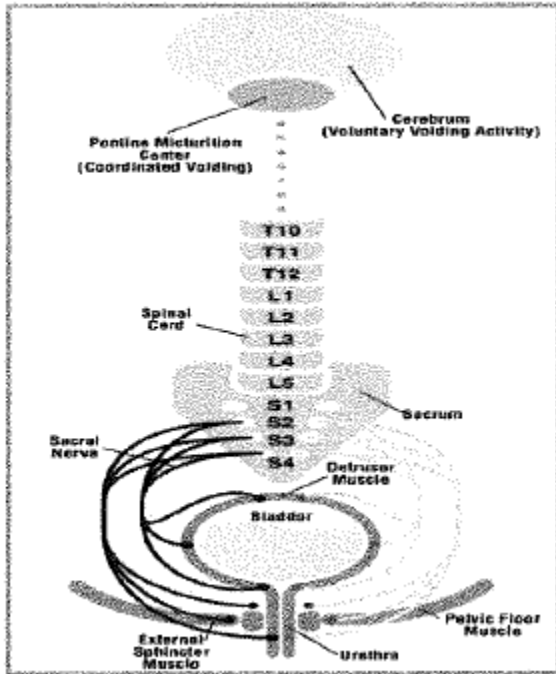
Urinary incontinence can result in minimal bother to life-altering distress. The amount of leakage does not always correlate to the degree of distress experienced by a woman. Age, body image, sexual activity, level of limitation, and physical discomfort from wet pads will all contribute to the burden that incontinence will become in a woman's life. In a study published in 2013, 1,050 women between the ages of 20 and 80 were asked to fill out the International Consultation of Incontinence Questionnaire-Short form. Thirty one percent

had SUI, 47% had UUI, and 33% had mixed incontinence. Ninety-five percent reported that the incontinence, specifically, had a negative impact on their quality of life, but only 35.3% had received any medical help for it.⁴⁶ The British Journal of Urology published a paper this year in which 1,730 patients from five different countries were asked about their Health Care Utilization (HCU) and Health Care Quality of Life (HCQoL) using validated questionnaires. In all parameters, incontinence patients reported statistically significant lower HRQoL and higher HCU, including use of surgeries, hospitalization, medications, pads, and medical visits.⁴⁷

Pelvic floor disorders, including stress urinary incontinence, affect sexual health. Successful intervention can often result in improvement in sexual function, but not always. There is a subset of patients in whom resolution of the pelvic floor disorder will not help or it may even worsen sexual health in women.⁴⁸ This is commonly known to pelvic floor surgeons. In a study looking at the bother factor for urinary incontinence in men and women published in 2014, SUI was the second most bothersome symptom in the study population, after urgency. Less bothersome were nocturia, postmicturition dribble, and UUI. Overall, incontinent women were more bothered by their condition than incontinent men.⁴⁹

A. Urinary Urgency Incontinence

Urinary urgency incontinence results from a neuromuscular disruption between the brain, the spinal cord, and the bladder. The brain inhibits the bladder from uncontrollable spasms by sending constant signals through the spinal cord and the pelvic nerves. Compromise of the inhibition results in "dis"-inhibition, and involuntary loss of urine.



The bladder muscle (the detrusor muscle), literally, spasms, resulting in the loss of urine. Depending on the strength of the pelvic floor muscles, a reflexive contraction of the sphincter can sometimes control the amount of leakage. If the spasm is particularly strong, no amount of voluntary muscle strength will be able to counteract the evacuation of urine. More common among the elderly, UII can occur in men and women at any age. The signals

between the brain, the spinal cord, and the receptors in the bladder can be compromised by age (the brain deteriorates), neurological diseases, such as stroke, spinal cord injury, and multiple sclerosis (the nerve signals travelling from the brain to the bladder are disrupted), and spinal cord issues, such as spinal stenosis.

Transient UII can occur with a urinary tract infection, a viral syndrome, postoperatively from any major surgery, or after pelvic reconstructive surgery, such as prolapse and incontinence repairs. Bladder irritation, especially from any inflammatory process can cause an otherwise quiet bladder to spasm, resulting in the loss of urine. Some women, especially elderly women, may have no other symptoms of a urinary tract infection except the sudden onset of urinary incontinence. Flooding the body with fluid, as we do with abdominal surgeries, can cause leakage because the bladder becomes inundated with boluses of fluid that will irritate the lining, resulting in loss of control. Regaining proper fluid balance will resolve the problem. After prolapse and incontinence repairs, the newly

positioned bladder and urethra can take time to coordinate emptying. UUI can occur up to 12 weeks after pelvic floor surgery. Rarely, it will persist beyond.

Diagnosing UUI is done through a thorough history and physical exam. The complaint clinches the diagnosis, "I leak just as I am about to reach the bathroom" or "I put the key in the door, and I have to dash to the bathroom." The presence of a neurologic disorder is explored, as are new symptoms that may have surfaced, suggesting the development of a condition such as Multiple Sclerosis. On physical exam, concomitant stress incontinence and pelvic floor prolapse can be identified. Urine analysis for blood and white cells will indicate whether a cystoscopy should be done to rule out bladder cancer, and a culture for infection. Post-void residual urine measurements are usually determined to be sure that the bladder is emptying properly. Once the diagnosis is made and all underlying conditions are excluded, UUI can be treated without any further testing.

Many practitioners will elect to perform urodynamic testing to document bladder function and the presence of unstable bladder contractions. Urodynamic studies are performed in the office with no special preparation and no anesthesia. A small catheter is inserted into the bladder and another goes into either the rectum or the vaginal. Water slowly fills the bladder as the pressures generated by the bladder are recorded on a computer. When the bladder is full, the patient voids, and the computer records the volume voided, the velocity of the urine as it comes out, and the post-void residual. Different readings can be obtained from the study that can help understand the underlying cause, guide the treatment, and follow changes in progress.

The algorithm for treating UUI is three-tiered. Behavior modification includes managing fluids around the availability of a bathroom, and not overdrinking. Drinking to lose

weight or to keep from eating will only make the leakage worse. Urinating at intervals or before leaving a restaurant or a friend's house may keep the bladder capacity below the critical volume at which the detrusor muscle spasms. Kegel contractions create a reflexive relaxation of the detrusor muscle and may inhibit the contraction for a few extra seconds, which may be enough to get to the bathroom. If these interventions fail, then medication can be added. Ten choices are available, including an over-the-counter patch, eight anticholinergic pills, and one beta-agonist pill. Determinants of the choice of medication include tolerance to side effects, efficacy, strength, presence of contraindicated conditions, cost, and insurance coverage. If two or more drugs fail to control the leakage to the satisfaction of the patient, botulinum toxin or neuromodulation can be offered.

Botulinum A toxin can be injected into the bladder through a cystoscope, either in the operating room with a small amount of sedation, or in the office using local lidocaine. Thirty injections of 1cc each totaling 100 international units of Botox are delivered throughout the bladder into the detrusor muscle. The effects last approximately six months, with 22.9% of the study population achieving complete continence. The main side effect is incomplete bladder emptying, which occurs in 5.4% of patients.⁵⁰ It can be repeated regularly with maintenance of its efficacy. Sacral nerve modulation involves placing a wire through the third sacral interspace on one side of the patient, attaching the wire to an internal battery, and stimulating the pelvic nerves unilaterally to control leakage. It is performed in the office first with a temporary wire and battery. If there is more than 50% improvement in the symptoms, the implant can be performed in the hospital under sedation. The battery gets changed every 5-10 years depending on the amount of energy needed to obtain the desired effect. Fifty six percent of patients were completely dry and 85% were improved at six months, according to

a prospective randomized control trial published in European Urology in 2000.⁵¹ Performing one technique on a patient does not preclude performing the other. If one does not work sufficiently, the other can be attempted. Either one can be coupled with behavior modification and medication.

B. Stress Urinary Incontinence

1. Background

In women with pure stress urinary incontinence, the organs of the lower urinary tract, including the bladder and the urethra are healthy. The problem lies with the support *under* the urethra. Because the urethra is not sitting on a strong backboard of support, it cannot close against a strong backboard in reaction to an increase in intra-abdominal pressure. In many cases, this lack of support extends along the undersurface of the bladder up to the cervix, resulting in the bladder descending into the vaginal canal (cystocele) and the cervix dropping as well (uterine prolapse). If the posterior vaginal wall is weak, a rectocele will result. If the patient has had a hysterectomy, she may have a prolapse of the cuff of her vagina, resulting in a vault prolapse or an enterocele. Each of these defects can occur independently in any given patient, or they can all occur in the same woman. If a woman presents with complaints of urinary leakage relating to activity, the practitioner will examine her to see if she has any of the concomitant conditions that we often see in women with stress incontinence, including a cystocele, rectocele, uterine decent, or an enterocele. Just because these defects are present does not mean that any or all of them need to be treated. The physician and the patient can determine together which approach is best in managing, first, her stress incontinence, and secondly, the other issues. There are women who have prolapse but no stress incontinence. Again, the same conversation would take place regarding the

need to manage a secondary concern (the stress urinary incontinence) when treating the most bothersome one.

2. Risk Factors and Diagnosis

Risk factors for the development of stress incontinence include pregnancy, vaginal delivery, chronic cough, constipation, heavy lifting, obesity, age, menopause, smoking history, prior pelvic surgery, pelvic organ prolapse, race and genetics.⁵²⁵³⁵⁴ Studies done on Sprague-Dawley female rats subjected to pudendal nerve crush and vaginal distension showed that external urethral sphincter pressures and leak point pressures were significantly altered. Interestingly, some of the rats recovered nerve function in the external sphincter. Their conclusion was that "although continence function recovered 9 weeks after simulated childbirth injury, innervation of EUS was not complete at this time point, suggestive of persistent neurogenic deficiency which when compounded by the effects of aging may lead to a delayed recurrence of SUI in this animal model with increased age."⁵⁵ In another study published in the BJOG in 2013, the authors reviewed the effects of a single vaginal delivery versus a single cesarean section 20 years postpartum. In the women who delivered vaginally, the incidence of UUI, SUI, and mixed urinary incontinence were all higher in the vaginal delivery group, as was the bother associated with all three types of urinary incontinence 20 years after delivery.⁵⁶

Stress urinary incontinence is diagnosed by history. Patients report leakage with activity and will often be able to quantify the amount of leakage based on the number of pads they wear. In order to avoid wearing pads at all, some women will urinate frequently, so that when they do something that may result in leakage, less urine will come out. Physical exam may or may not confirm the diagnosis. If the bladder is empty at the time of the exam, or the patient is lying supine, the examiner may not see the incontinence. Most treaters like to

witness the leakage before instituting therapy, especially if invasive treatments are offered. Filling the bladder with 50 or 100cc of sterile water and asking the patient to cough while standing will usually induce the leakage. Urine analysis is done to rule out infection, and postvoid residual will help determine if the patient has overflow. Because mixed incontinence is so common in women with stress incontinence, urodynamic testing may be done to identify intrinsic bladder issues that may complicate the management of stress incontinence. Because many women who suffer from SUI void often, they don't let their bladders fill to point where they would notice urgency incontinence. Urodynamics would elucidate detrusor spasms that may not be clinically apparent to the patient. The AUA guidelines state "the evaluation of the index patient should include the following components": focused history, focused physical examination, objective demonstration of SUI, assessment of postvoid residual urine volume, and urinalysis, and culture if indicated. The guidelines further recommend that "[a]dditional diagnostic studies can be performed to assess the integrity and function of the lower urinary tract." These tests may include pad testing and/or voiding diary, urodynamics, cystoscopy, and imaging.⁵⁷ Once the diagnosis is made and concomitant pathology, including UUI, mixed incontinence, and pelvic floor prolapse are evaluated, treatment can be offered.

3. Treatment

Treatment options for stress urinary incontinence include: physical therapy and pelvic floor strengthening exercise, bulking agents, and surgery (midurethral slings made of autologous fascia, cadaveric fascia, biologic material, or synthetics). Placement of slings can be retropubic or transobturator.

Pessaries are not used to treat stress urinary incontinence. They are effective in the conservative management of anterior wall prolapse and uterine prolapse. In many cases, they

make stress incontinence worse because the bladder is mechanically lifted, creating a straight line of trajectory for the urine. Attempts at creating a pessary that will help manage stress incontinence have been unsuccessful, leading to obstruction and poor emptying.

a. Physical Therapy

Pelvic floor physical therapy includes the effective performance of kegel exercises, either passively through electrical stimulation or actively using biofeedback, vaginal inserts, or external thigh and buttock strengtheners. The pubococcygeus muscles are generally considered the voluntary muscles that can control urination. The ideal pattern, frequency, and duration of an exercise program to treat stress urinary incontinence has never been determined. There is consensus that the more effectively and the more frequently the exercises are done, the better the results. Biofeedback machines provide a means by which women can ensure that they are performing the exercises correctly. If a woman has pelvic muscles that are too weak to even initiate a contraction, or if a woman cannot coordinate the muscles enough to effectively squeeze the pubococcygeus muscle, then electrical stimulation can be used. Passive contraction of the muscle using a probe attached to a battery will force the muscle to spasm.

In 2013, a study performed in the Netherlands comparing physiotherapy to surgery for the treatment of SUI was published in the New England Journal of Medicine. Patients were randomized to either midurethral synthetic sling surgery or physical therapy with 196 in the surgery group and 174 in the therapy group. Nearly 50% of the therapy group crossed over to the surgery group before the 12-month study period was completed. Improvement rates among the surgery group were over 90% at one year and 64% in the physiotherapy group. Eighty-five percent of the sling patients reported no stress incontinence at the end of the study while 65% of the physiotherapy group were symptom free. The authors conclude "the results

of our trial show that women with moderate-to-severe stress urinary incontinence have significantly better subjective and objective outcomes at 12 months after surgery than after physiotherapy."⁵⁸

b. Bulking Agents

Considered a minimally invasive option, the injection of periurethral bulking agents has been used for decades to increase the closure pressure of the urethra. The procedure is performed through a cystoscope under direct vision, or through a needle placed next to the urethra. Materials that have been used include collagen, autologous fat, silicone particles, calcium hydroxyapatite, ethylene vinyl alcohol, dextronomer hyaluronic acid and carbon spheres. A study published in 2007, and then updated in 2012, identified 12 trials of a total of 1,318 women who had undergone injection of one of these agents. Because the studies had so many variables, meta-analysis was not appropriate. Safety concerns led to the termination of a study looking at autologous fat injections. Injection site complications led to dextronomer hyaluronic acid being pulled from the market. Nearly all of the materials resulted in the same poor efficacy and durability as collagen. The authors conclude, "The finding that placebo saline injection was followed by a similar symptomatic improvement questions the mechanism of any effects." No studies have compared injection therapy with physical therapy. In comparison to surgery, all of the bulking agents did poorly.⁵⁹

Patients considering collagen injections need to undergo a skin test before periurethral insertion can be considered to be sure that there will not be an allergic reaction. The urethral injection lasts approximately six months before it needs to be repeated. The only advantage to the use of bulking agent is its potential injection in the office with no anesthesia. This option is reserved for two categories of patients: (1) those who have stress incontinence, are poor surgical risks, and desire temporary relief of their leakage for a special occasion, like a

wedding or family cruise, and (2) those who have slight incontinence after a sling surgery and would like complete resolution. Researchers continue to explore materials that would make an ideal seal around the urethra. The challenges of finding an ideal agent include providing a delivery system, identifying a durable material, and preventing migration. Stem cells have been an interesting area of exploration as a bulking agent that may satisfy all three criteria.

c. Surgical Treatment of SUI

1) History

Surgery to treat stress urinary incontinence did not become routine until around 1900 when Kelly popularized imbrication of the anterior vaginal wall and the bladder neck, using mattress sutures. This technique became the accepted method of treating stress urinary incontinence for the next 60 years. In 1907, the first retropubic sling was performed using a piece of gracilis muscle, as described by Von Giardano. Aldridge studied the vaginal approach to incontinence surgery and recognized that suburethral support is the best way to achieve continence. However, complications due to inadequate response of the harvested tissues in the periurethral space delayed the development of acceptable procedures.⁶⁰ The modern urethropexy was introduced by Marshall-Marchetti-Krantz in 1949 and modified by Burch in 1961. Peyrera popularized the transvaginal approach in 1959, with Stamey introducing cystoscopic guidance in 1973. Mullen introduced autologous pubovaginal sling surgery in 1947. He harvested rectus fascia and inserted it under the urethra through a transvaginal approach. McGuire and Blaivas advanced the technique of the rectus fascia sling.

In an effort to provide good results in patients with poor native tissue, Zoedler and Boeminghous introduced the first synthetic slings in the early 1960s. The first

materials that were used, including Marlex, Gortex, and Mersilene, resulted in complications such as abscess formation, transection of the urethra, shrinkage of the mesh, and urethral obstruction. Ultimately, in the 1990s polypropylene mesh was identified as the most biocompatible synthetic material available for vaginal surgery, due to its flexible weave and large pore size. The majority of the stress incontinence surgeries that are performed today involve a polypropylene mid-urethral sling.

In 2013, Chughtai et al. published data in which the operative logs of urologists applying for recertification were analyzed regarding their preferences for female stress incontinence surgery. Nearly two-thirds of the 6,355 applicants reported performing incontinence surgery on women, with the majority of the procedures being synthetic midurethral slings. The number of traditional repairs decreased from 17% to 5% between 2003 and 2004. In 2010, less than 1% of incontinence surgeries performed involved autologous slings.⁶¹ A study looking at vaginal mesh use by pelvic surgeons after the 2011 FDA safety update found that of the 53% of AUGS members who responded, over 99% used mesh for incontinence treatment before the warning and there was no significant change in their use after.⁶² Finally, in a study evaluating the utility of urodynamics in the evaluation of patients with stress urinary incontinence, the surgery of choice for the 630 patients enrolled was a synthetic midurethral sling, either transobturator or retropubic. By 2012, when the study was published, the material of choice was the synthetic midurethral sling.⁶³

2) Autologous Fascia Slings

Autologous fascial slings involve harvesting a piece of fascia from the patient, fashioning it into a strip, and placing it under the urethra. The most popular donor site is the anterior rectus fascia in the lower abdominal wall. A Pfannestiel incision is made to expose

the rectus sheath, a 10 cm x 1 cm strip of tissue is dissected free, and the incision is closed. An absorbable suture is placed through either end of the strip of rectus tissue and the sling is then passed through the retropubic space on either side of the urethra through a vaginal incision. The procedure takes 1-2 hours and involves two incisions: the vaginal incision for placement of the sling, and the abdominal incision for the harvesting of the fascia.

Studies comparing autologous slings to the Burch colposuspension, which was considered the standard of care for decades, declared the autologous sling to be both more successful and more morbid. The Urinary Incontinence Network published an article in the New England Journal of Medicine in 2007 in which 520 patients were randomized to either the autologous fascial sling or the Burch. At two years, the sling group reported 66% continence rates, while the Burch group reported 49%. However, the sling patients suffered from more complications, including urinary tract infections, difficulty voiding, and new-onset urgency incontinence.⁶⁴ These results were confirmed in a follow-up study published in the Journal of Urology in 2009. The authors reported higher complication rates with autologous sling surgery, which they could attribute directly to the surgery and not patient factors.⁶⁵ Five-year data published in 2012 reported dismal continence rates for both procedures. Twenty-four percent of the Burch group were still continent while 30.8% of the autologous sling group were dry.⁶⁶ Seven-year data showed a continued decline in continence rates: 13% of the Burch group and 27% of the autologous sling group were dry.⁶⁷ In 2013, Zimmern reported 76% improvement in continence in 110 patients who underwent autologous sling surgery, some of whom were on their second attempt at repair.⁶⁸ In an article published in 2013, the authors reported on their comparative results of approximately 200 patients who underwent an autologous fascial sling and 200 patients

who had a transobturator synthetic sling. At two years, the efficacy of both groups was the same at 86%, but the complication rate was nearly 25% for the autologous sling group versus 14% for the transobturator group. The autologous fascia sling took one hour and 29 minutes longer to perform than the autologous sling (112 minutes versus 23 minutes).⁶⁹ Even if the continence rates and risk of complications is considered acceptable for autologous slings, the increased operative time and the unsightly scar that the harvest site leaves has led to efforts to find better options for patients. Cadaveric fascia lata, bovine pericardium, xenograft tissues, and anterior vaginal wall slings have all been used to treat stress urinary incontinence with poor outcomes and insufficient durability. In 2001, I published a study in which we reviewed our data looking at the results of 154 patients who had undergone cadaveric fascial slings using bone anchors, of whom 37% had recurrent symptoms and 17% consented to a second operation at less than one year.⁷⁰ Synthetic materials were introduced in the 1960s and have finally become the option of choice for stress incontinence surgery.

3) Synthetic Slings

Papa Petros and Ulmsten introduced the polypropylene midurethral sling (MUS) into the literature in 1993. In 1998, they published their preliminary results in which 119 patients were implanted with the TVT under local anesthesia. Ninety-one percent of their patients were cured at one year and another 7% were improved. Ninety percent of them went home the same day. Three patients went home with the catheter for three days, and one kept it for ten. Three patients had a hematoma and one patient's bladder was perforated. All of the complications were resolved without further surgery or transfusion.⁷¹ Since that initial paper, hundreds of peer-reviewed papers have been published looking at the safety and efficacy of TVT and TVT-O.

Trials at ten years, 11 years, and 17 years all support the use of TVT in the treatment of SUI. Serati et al. reported at the European Association of Urology in 2012 that of the 63 patients in whom they originally implanted, 58 of them were available for 10-year follow-up. Objective cure rates, defined by the absence of leakage on cough test, were 89.7% and subjective cure rates were 93%. Thirty percent of the patients reported de novo (new onset) of urgency incontinence at three months, but only 18.9% had it at ten years. As noted earlier, urgency incontinence is a condition that is prevalent and many women develop it every year regardless of sling surgery. None of the patients reported dyspareunia or were found to have eroded mesh on examination.⁷² Another ten-year prospective study followed 603 women, of whom 483 were available for follow-up. The objective cure rate was 89.9%. Nine of the 483 (2%) patients who failed their original TVT underwent a second one. In this study, the de novo urgency incontinence rate after surgery was 4.1% at one year and 14.9% at 10 years. Of course other factors may have contributed to the onset of urgency symptoms ten years after surgery, especially aging. The mesh exposure rate immediately after surgery was 0.6%, and none at ten years. The presence of voiding difficulties, such as slow stream and elevated residuals, did not translate into subjective bother. Patients with residuals up to 100cc or slow stream at ten years were equally as satisfied as those who did not show those changes, with 83% satisfaction all around.⁷³ Finally, a study of 60 patients found that, of the 52 who were available at ten years, 77% reported that the surgery had either cured their problem or improved it. Ten percent had de novo urgency incontinence. Patients with impaired bladder emptying reported the most unfavorable subjective results.⁷⁴ Tensioning issues would account for difficult emptying.

Eleven-year data published in the International Journal of Urogynecology in 2008 reported 90% of the women available for follow-up had both subjective and objective cure rates, as defined by a negative pad test and no leakage with coughing. None of the patients had mesh extrusion and 93% of the patients had post-void residual urine measurements below 100cc. Ninety-seven percent "were prepared to recommend the surgery to a friend."⁷⁵ In 2010, another study prospectively followed up patients at 11 years and found that 84% of them were objectively cured, and 96% were either subjectively cured or improved. Twenty-one patients experienced de novo urgency incontinence, but 13 of the original 24 who presented with urgency incontinence preoperatively got better. One patient in the original series had mesh exposure and none developed it during the 11 years of follow-up.⁷⁶ Twelve-year data published in 2012 reported on 107 patients. Ninety-three percent of the original patients had a negative stress test. Of the patients who failed, one patient had another TVT implanted and the other five had a TVT-O. One patient had her sling cut at one year for retention, and one, at eight years, due to pain. Resolution of symptoms occurred in both instances. No mesh extrusions into the vaginal wall were reported, and one patient had eroded mesh in her bladder that was resected.⁷⁷ Finally, 17-year data on 78% of the original study cohort was published in 2013. Over 90% of the women were objectively cured and 87% were subjectively cured or improved. One patient was found to have an asymptomatic extrusion on exam. "No other tape complications occurred."⁷⁸

Concerns about the potential for bowel and bladder perforation (3-6%), the need for retropubic dissection, and the increased hematoma formation (1-3%) in the performance of retropubic stress incontinence surgery, led to an effort to find an even more minimally-

invasive procedure than TVT.⁷⁹ In 2001, Delorme introduced the outside-in, tension-free transobturator tape (TOT). In 2003, De Leval developed the inside-out approach of placing the sling through the obturator foramen. His one-year data looking at 99 patients who were implanted with TVT-O showed a 91% cure rate for stress incontinence. None of the patients had mesh erosion. Four of the 99 patients needed the tape to be released due to voiding difficulty, with resolution of their frequency and urgency.⁸⁰ The excellent cure rates and minimally invasive profile demonstrated in this study has been replicated in numerous other series and randomized controlled trials.

The mesh that is used in the TVT-O is the same as that used in TVT. Wide- weave polypropylene mesh is fashioned into a strip that is left under the urethra of the woman suffering from stress urinary incontinence. Whether the insertion is performed retropubic or transobturator does not change the characteristics of the mesh or the way in which the patient's tissues will react to the mesh. The difference in the two procedures is: (1) the delivery system of the kit, and (2) the trajectory of the mesh in relation to the urethra. The TVT is delivered through the retropubic space with specific instruments that do not impact on the patient's anatomy or results, as long as they are used correctly, which is surgeon-driven. The instruments are standard tools, well-recognized, and widely used by any trained pelvic surgeon. The mesh sits in a "U" shape under the urethra, and needs to be tensioned specifically for that configuration. The surgeon determines the tensioning, a technique that is taught to residents throughout their training in female pelvic surgery, regardless of the kit or the device that is used. The same technique is used for tensioning all retropubic slings, whether they are done using the TVT kit, another retropubic kit, or a self-styled retropubic sling using synthetic mesh or autologous fascia.

The transobturator technique involves placing a supportive material under the urethra in a hammock-formation. Again, if a kit is used, the instruments that come with the kit do not remain in the patient. Tensioning of the transobturator sling, like that for fascial and other retropubic slings, is at the discretion of the surgeon and is different for different patients. The TVT-O is a type of sling kit in which the same mesh as is used in the TVT is placed through the obturator foramen using disposable instruments that are packaged with the mesh. Again, the method of placing the mesh, the delivery system, the space in which it passes, and the shape in which it lays differ between TVT and TVT-O, but not the mesh itself. The TVT and TVT-O kits include the same mesh.

Three-year data comparing TVT and TVT-O in a randomized prospective study showed that 94.6% of the TVT group and 89.5% of the TVT-O group were objectively cured. Subjective cure rates were the same between the two groups at 90%. No mesh extrusions were seen in either group at three years, although one patient in the TVT-O group had an extrusion at one year and needed the tape removed. Subsequently, she had a TVT done for recurrent SUI. De novo urgency incontinence occurred in 9.2% of the TVT group and 5.6% of the TVT-O group. At three years, prophylactic antibiotic use was needed in one patient in the TVT group and five patients in the TVT-O group because of recurrent urinary tract infections. Over 90% in each group would offer the operation to a friend.⁸¹ Four- year data looking at TVT-O alone (74 patients) and TVT-O in conjunction with anterior colporrhaphy (41 patients) shows that the procedure works successfully in over 85% of the patients whether they have a cystocele repair done at the same time or not. One patient in each group had a mesh extrusion, both of which were identified within the first five months from surgery. The mesh was removed in both cases. Seven patients who had the TVT-O had

urinary retention, but only one of the seven needed the tape cut, and she remained both continent and voiding with low residuals thereafter.⁸²

Three prospective studies looking at five-year outcomes of patients with TVT-O showed durability of the procedure without long-term complications. In a study out of China, 87% of the 103 patients entered had complete resolution of their SUI at one year and five years. One patient had tape erosion, which was removed, and 25 had leg pain. All but three of the patients with leg pain had spontaneous resolution at one year.⁸³ Similar results were reported in European Urology in which 191 women were followed prospectively for five years. Objective and subjective cure rates were over 90% with de novo urgency incontinence rates of 24%. These patients received medication, Botox injections, or Tibial nerve stimulation. No long-term mesh extrusion was identified.⁸⁴ Finally, a study published in Journal of Women's Health found an improved/cure rate of 82% at five years. None of their patients had de novo urgency incontinence or erosions. Interestingly, 72% of their study population had overactive bladder symptoms preoperatively, which may account for their slightly lower cure rates. Distinction between failure due to recurrent stress urinary incontinence or urinary urgency incontinence is not made clear in the data.⁸⁵ Seven-year data shows that the cure rate is durable at over 80% both objectively and subjectively. De novo urgency incontinence was reported to be 7% in this study and the extrusion rate was zero. Over 70% of the patients in this study had a concomitant pelvic floor repair, which may have impacted the data.⁸⁶

A series of meta-analyses have been performed to assess the data comparing synthetic mid urethral slings, including TVT and TVT-O, to autologous fascial slings, and Burch colpopexy. In 2009, Ogah conducted a Cochrane review of randomized controlled

trials comparing different types of pubovaginal slings with different types of synthetic midurethral slings. Sixty-two studies were included in the analysis. Nine trials looking at synthetic midurethral slings versus traditional slings found that the outcomes and adverse events were the same for both groups. There was no difference in postoperative voiding dysfunction but there was less de novo urgency incontinence in the synthetic midurethral sling group. The main difference between the two groups was the mean operative time: 35 minutes for the MUS group and 87 minutes for the pubovaginal sling group. Nine trials comparing synthetic midurethral slings versus open Burches showed no difference in cure rates at one year but the Burch group was more likely to develop prolapse in the future. Again, the de novo urgency incontinence rates were the same for both the Burch and the midurethral sling group but the operative time and length of hospital stay was considerably longer for the open Burch procedure, as was the overall cost of the procedure. The midurethral sling group had 3% erosion rate and a 6% incidence of bladder perforation.⁸⁷ In 2010, Novara reported the results of an extended meta-analysis comparing the midurethral sling procedure with the Burch and pubovaginal sling. The cure rates were the same across all three procedures, although none of the studies that they reviewed went beyond five years. Complication rates were higher in the pubovaginal sling versus the midurethral sling group with more reoperations and urgency incontinence.⁸⁸ In 2011, Rehman et al. found that pubovaginal sling surgery resulted in more complications than when a mid-urethral sling is performed. Increased postoperative voiding dysfunction and -operating time in the pubovaginal sling papers favored performance of a MUS for SUI.⁸⁹ In 2014, Schimpf et al. reported that, when comparing pubovaginal slings versus to midurethral slings, subjective cure

was higher with midurethral slings. As a result, the authors recommended midurethral slings over pubovaginal slings.⁹⁰

Several randomized control trials comparing retropubic synthetic midurethral slings with transobturator midurethral sling have all shown clinically similar success with retropubic slings but also a higher complication rate than when the transobturator approach is used. The cure rates up to five years hover around 85% for both groups. Bladder perforations, bleeding, and postoperative voiding dysfunction were more common in the retropubic approach. De novo urgency and mesh erosion were the same in both groups. The overall conclusion is that the transobturator approach offers the efficacy of the retropubic approach without some of the potential complications.⁹¹⁹²

As a result of the robust body of evidence that has come out of the literature in the last ten years regarding the safety and efficacy of transvaginal synthetic slings, the American Urological Association, the American Urogynecologic Society, SUFU, ACOG, the National Institute of Health and Care Excellence (NICE), and other specialty organizations have all issued statements in support of synthetic midurethral slings as the surgical treatment of choice for the treatment of stress urinary incontinence. For example, the AUA has stated, "extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low."⁹³ In the AUA patient brochure sponsored by the Urology Care foundation, called "It's time to talk about SUI", the recommendation if surgical treatment is considered

is a sling. "The sling can be made from biologic or synthetic materials."⁹⁴ As the organization that represents 1,300 Female Pelvic Medicine and Reconstructive Surgeons, the American Urogynecologic Society opposes any restrictions on the use of vaginal mesh imposed by healthcare systems, state and local medical organization, and malpractice insurance companies. They state that all of the available surgical materials should be available for use at the discretion of the surgeon and the patient.⁹⁵ In September of 2013, the National Institute for Health and Care Excellence published their recommendations for the surgical treatment of stress urinary incontinence in women, including "using devices in which there is current high quality data, devices in which the surgeon is trained, slings made of macroporous polypropylene mesh, and materials that are colored for easy visibility in case of an extrusion or revision."⁹⁶ The TVT mesh is a proven mesh; it has been studied more than any other SUI mesh in women with the condition and data goes out to 17 years. In 2014, the American Urogynecological Society and the Society of Urodynamics and Female Pelvic Medicine and Urogenital Reconstruction put out a joint statement supporting synthetic midurethral slings as the gold standard for the surgical treatment of female stress urinary incontinence.

V. My Personal Experience Using Mesh

I learned to use vaginal mesh during my one-year fellowship in 1999 with Dr. Shlomo Raz. During that year, we reviewed his pubovaginal sling data using cadaveric fascia secured with bone anchors for the treatment of female stress urinary incontinence. We found that 37% of the patients failed, some within the first year of surgery.⁹⁷ In response to those poor results, we started to cut a strip of polypropylene mesh from a stock piece of hernia mesh. Absorbable sutures were threaded through each end and we passed the sling through the retropubic space, tying the sutures above the pubic bone and tensioning the mesh under the

urethra. In addition, we were using mesh to reinforce our cystocele repairs after placating the pubocervical fascia.

In my early years of practice, I continued to fashion my slings, as I had learned in fellowship. For prolapse surgery, I stopped imbricating and simply secured a loose piece of mesh under the bladder in a technique that was presented at the AUA in 2008.⁹⁸ When Gynemesh became available in 2002, I switched from hernia mesh for both my self-styled slings to the Gynecare product because of its wider pores and more flexible weave. Although I was not an early adopter of the kits, I was an early user of transvaginal mesh. By utilizing good surgical principles, I was getting durable results, with less dissection than is necessary for a native tissue repair, and very few complications. Full thickness skin flaps, hemostasis, and smooth placement of the mesh resulted in a reduction of mesh extrusion to less than 5%.

In 2005, after performing prolapse surgery using mesh for five years as an attending surgeon, I learned to implant Prolift because it offered advantages that I could not implement without its unique design. My Prolift training involved a didactic lecture and observation in the operating room of an experienced Prolift implanter. Because I had so much experience performing vaginal prolapse repairs, the learning curve for me to integrate Prolift into my practice was not difficult. I had done over a 1000 prolapse repairs by the time Prolift was introduced, and I have done approximately 500 repairs using Prolift since that time.

In 2006, I learned to implant TVT-O. The technique for passing the trocars through the obturator foramen is the same for TVT-O as for the anterior straps of the Prolift kit. I attended a cadaver lab sponsored by Gynecare and began to use TVT-O in my practice. At the course I attended, I read the IFU that was provided with the kit, which offers suggestions on surgical technique and warnings, many of which are routine for all sling surgery.

I have not encountered roping, curling, degradation, or particle loss of mesh in my practice, unless it has been improperly placed. Moreover, the mesh does not contract or collapse when placed according to the IFU. Tissue that forms after pelvic surgery contracts, but the mesh itself does not contract.⁹⁹¹⁰⁰ Additionally, in my experience and in the medical literature, both laser-cut and mechanically-cut Prolene mesh have proven safe and effective.¹⁰¹¹⁰² I have found no practical difference between the two in my practice. The suggestion that Ultrapro or Gynemesh PS is a safer mesh than Prolene mesh in an SUI indication is unsupported. The Okulu study sometimes cited by plaintiffs' experts for that proposition does not use TVT mesh as a comparator, involves a mesh that is not shaped like TVT, and involves a technique completely different than the one used to implant the TVT or TVT-O slings.¹⁰³

VI. Complications

Many of the warnings stated in the IFUs for mesh kits have nothing to do with TVT-O or Prolift in particular. Those warnings are true for any surgery. Avoidance of nerves, large blood vessels, the bladder, and the bowel is sound surgical advice for placing any sling, whether it be a synthetic or an autologous sling. Observing patients postoperatively for bleeding, having the patient call with any problems after surgery, and avoidance of lifting and intercourse are typical instructions for any pelvic surgery. De novo urgency incontinence, infection, and recurrence are well-known side effects of any pelvic operation. Transient leg pain is unique to TVT-O, and patients are instructed of that eventuality.

Mesh extrusion is another well-recognized complication of mesh surgery, including TVT-O and Prolift. If it occurs, it may require a revision or replacement of the mesh. Patients in my practice are counseled about both of those possibilities.¹⁰⁴ In cases in which I have re-operated on women who have had vaginal mesh placed, I have not found the surgical field difficult to manage. Mesh extrusions are removed by releasing the un-integrated exposed piece

of mesh. The rest of the mesh that is not exposed is integrated and completely revascularized by the host. It is not necessary to remove the remaining mesh. It has become part of the patient. I have not had the experience of mesh migrating, eroding into neighboring organs, or fragmenting nor does the medical literature bear these out as significant risks. It is not a biologically active material, so it cannot come alive. However, it does provide a scaffold for ingrowth of tissue that is alive, enervated, and strong.

It is my opinion that the IFUs for TVT-O and Prolift are adequate to inform surgeons who would be doing the procedure of the potential risks. The information in the IFUs are further supplemented by professional education, such as that I attended, and which is recommended in the IFUs. The professional education programs are well done, helpful to surgeons who choose to undergo them, and are consistent with other forms of education that surgeons undergo in their professional development. Consistent with medical training, didactic lectures and cadaver labs are taught in medical school and residency and continue to be offered through professional organizations like SUFU, AUA, and AUGS.

Regardless of the philosophical or theoretical risks, the safety and durability of mesh has been borne out by the literature and my personal experience with patients. The TVT-O and Prolift kits are safe and effective and they are not defective in my opinion. They are state of the art and the standard of care, for the surgical treatment of POP and SUI with a favorable benefit-to-risk profile. In particular, full length slings like TVT-O are the gold standard treatment for SUI with a vast body of clinical literature supporting their use.

OPINIONS:

1. Gynecare Prolift and TVTO are safe and effective products supported by a substantial body of clinical data. Prolift was an appropriate treatment option for many women who were suffering from pelvic organ prolapse, and substantially advanced the treatment of prolapse surgery. Midurethral slings, including TVT-O, are considered the “gold standard” for the management of stress urinary incontinence. Based on my extensive experience of implanting Prolift and TVT-O in patients, and managing their post-operative care, my review of the medical literature, and my training, it is my opinion that these products are not defectively designed.

2. The mesh used in the Prolift and TVTO is a safe and effective material for use in these indications. Polypropylene mesh and polypropylene sutures have been in surgical use for decades. Based on my extensive experience in implanting these devices and managing the post-operative course of patients, it is my opinion that the pore size of the mesh used in these products is appropriate to allow for the proper tissue incorporation.

3. A foreign body/inflammatory response is an expected and physiological outcome of the placement of any surgical implant. This response does not have a negative, clinical impact on clinical outcomes when the mesh is placed correctly. The acute response to the implant includes fibroblast and macrophage infiltration, angiogenesis, and inosculation of new tissue. The long term response to the synthetic graft is integration of the mesh fibers into the new tissue that has been laid down by the body. New blood vessels, nerve fibers, and connective tissue grow between within the mesh, creating a new, strong support for the pelvic floor structures. It is not meant to be removed or modified once it is implanted.

4. The extensive clinical data on Prolift and mesh slings knitted of PROLENE® (TVT, TVT-O) does not demonstrate that the mesh in these products degrades in the human body in any manner that has a clinical impact on women.

5. If Prolift is placed tension-free as described in the IFU and as can be seen in professional education materials, contraction seldom has clinical implications for the patient. It is clear from a large body of evidence that dyspareunia rates after Prolift and other mesh repairs are consistent with and in some cases lower than the dyspareunia rates after a variety of native tissue repairs for prolapse, in which no implant material is used.

6. The medical literature does not demonstrate that the mesh implant in TVT-O migrates if it is implanted in accordance with the procedure set forth in the IFU.

7. There is no evidence to suggest that the manner in which TVT-O mesh is cut (mechanical v. laser) has a clinical impact on patients.

8. The potential risks of Prolift and TVTO are appropriately described in their respective IFUs and Ethicon professional education materials, particularly when taking into consideration the base of surgical and anatomic knowledge held by a surgeon who has been trained to use the product, which is explicitly referenced in the IFU.

9. Alternative options available to patients with high grade prolapse who want a vaginal repair do not have the same efficacy as repairs done with Prolift mesh. If synthetic mesh is not used, inferior options with lower efficacy and higher morbidity must be utilized.

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